



## Complete Summary

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### GUIDELINE TITLE

Management of hepatocellular carcinoma.

### BIBLIOGRAPHIC SOURCE(S)

Bruix J, Sherman M, Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005 Nov; 42(5): 1208-36. [322 references] [PubMed](#)

### GUIDELINE STATUS

This is the current release of the guideline.

## COMPLETE SUMMARY CONTENT

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## SCOPE

### DISEASE/CONDITION(S)

Hepatocellular carcinoma

### GUIDELINE CATEGORY

Diagnosis

Evaluation

Management

Prevention

Screening

Treatment

### CLINICAL SPECIALTY

Gastroenterology  
Infectious Diseases  
Internal Medicine  
Oncology  
Pathology  
Radiation Oncology  
Surgery

## INTENDED USERS

Advanced Practice Nurses  
Physician Assistants  
Physicians

## GUIDELINE OBJECTIVE(S)

To provide a data-supported approach to the surveillance, diagnosis, staging, treatment and management of hepatocellular carcinoma (HCC)

## TARGET POPULATION

Patients with hepatocellular carcinoma, and patients at high risk for the development of hepatocellular carcinoma, including patients in the following groups:

- Patients with chronic hepatitis B infection (positive hepatitis B surface antigen)
- Patients with cirrhosis due to
  - Hepatitis C
  - Alcohol use
  - Genetic hemochromatosis
  - Primary biliary cirrhosis

Note: Patients with cirrhosis due to alpha 1-antitrypsin deficiency, non alcoholic steatohepatitis or autoimmune hepatitis are not covered by this guideline.

## INTERVENTIONS AND PRACTICES CONSIDERED

### Surveillance/Screening

1. Identification of high-risk patients
2. Surveillance (screening) tests
  - Serological tests such as tests for alphafetoprotein (AFP) (Note: testing des-gamma-carboxy prothrombin [DGCP] is considered but not recommended)
  - Radiological tests such as ultrasonography (computed tomography [CT] scans are considered but not recommended)
  - Combined AFP and ultrasound testing
3. Length of surveillance interval
4. Surveillance of patients on the transplant waiting list for hepatocellular carcinoma (HCC)

## Diagnosis and Staging of HCC

1. Testing based on size of lesion
  - Imaging studies such as ultrasound, CT scan, contrast ultrasound, or magnetic resonance imaging (MRI) scan with contrast
  - Biopsy with evaluation by expert pathologist
2. Tumor staging
  - TNM system
  - Okuda system
  - Barcelona Clinic Liver Cancer (BCLC) staging system

## Treatment/Management

1. Surgical resection
  - Pre- or post-resection adjuvant therapy (considered but not recommended)
2. Liver transplantation
  - Cadaveric liver transplantation
  - Living donor liver transplantation
  - Priority listing for transplantation
  - Preoperative therapy
3. Percutaneous ablation
  - Alcohol injection
  - Radiofrequency ablation
4. Transarterial embolization and chemoembolization

Note the following treatment options are not recommended: Tamoxifen, antiandrogens, octreotide, hepatic artery ligation/embolization or systemic or selective intra-arterial chemotherapy. In addition, radio-labeled Yttrium glass beads, radio-labeled lipiodol or immunotherapy cannot be recommended as standard therapy for advanced HCC outside clinical trials.

## MAJOR OUTCOMES CONSIDERED

- Sensitivity, specificity, and predictive value of screening and diagnostic tests
- Risk for and incidence of hepatocellular carcinoma
- Cost-effectiveness of tests and procedures
- Organ wait-list dropout rate
- Tumor recurrence rate
- Disease-related mortality
- Treatment-related mortality
- Overall survival duration
- Disease-free survival
- Tumor necrosis rate

## METHODOLOGY

## METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)  
Hand-searches of Published Literature (Secondary Sources)  
Searches of Electronic Databases

#### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

These recommendations provide a data-supported approach to the diagnosis, staging and treatment of patients diagnosed with hepatocellular carcinoma (HCC). They are based on the following: (a) formal review and analysis of the recently-published world literature on the topic (Medline search through early 2005); (b) American College of Physicians Manual for Assessing Health Practices and Designing Practice Guidelines. (c) guideline policies, including the American Association for the Study of Liver Diseases (AASLD) Policy on the Development and Use of Practice Guidelines and the American Gastroenterology Association (AGA) Policy Statement on Guidelines; (d) the experience of the authors in the specified topic. Also reviewed were the guidelines prepared at the time of the Monothematic Conference of the European Association for the Study of the Liver (EASL) and the practice of authors experienced in the field.

#### NUMBER OF SOURCE DOCUMENTS

Not stated

#### METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

#### RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence According to Study Design

I: Randomized controlled trials

II-1: Controlled trials without randomization

II-2: Cohort or case-control analytic studies

II-3: Multiple time series, dramatic uncontrolled experiments

III: Opinion of respected authorities, descriptive epidemiology

#### METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses  
Systematic Review

#### DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Informal Consensus

## DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

## RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

## COST ANALYSIS

### Cost-effectiveness of Surveillance

An intervention is considered effective if it provides an increase in longevity of about 100 days (i.e., about 3 months). Although the levels were set years ago, and may not be appropriate today, interventions that can be achieved at a cost of less than about \$50,000/year of life gained are considered cost-effective. There are now several published decision analysis/cost-efficacy models for hepatocellular carcinoma (HCC) surveillance. The models differ in the nature of the theoretical population being analyzed, and in the intervention being applied. Nonetheless, these models have several results in common. They all find that surveillance is cost-effective, although in some cases only marginally so, and most find that the efficacy of surveillance is highly dependent on the incidence of HCC. (Refer to the original guideline document for a short description of these models). Thus, for patients with cirrhosis of varying etiologies, surveillance should be offered when the risk of HCC is 1.5%/year or greater. A table in the "Major Recommendations" section of this summary (Table 3 in the original guideline document) describes the groups of patients in which these limits are exceeded. These groups of patients are also discussed in more detail in the original guideline document. These cost-efficacy analyses were restricted to cirrhotic populations.

The above cost-efficacy analyses, which were restricted to cirrhotic populations, cannot be applied to hepatitis B carriers without cirrhosis. These patients, particularly in Asia and Africa, are also at risk for HCC. A cost-efficacy analysis of surveillance of hepatitis B carriers using ultrasound and alpha-fetoprotein (AFP) levels suggested that surveillance became cost-effective once the incidence of HCC exceeded 0.2%/year.

It would seem to be in a patient's interest to have a small HCC diagnosed while on the liver transplant waiting list. One cost-efficacy analysis has suggested that the increase in longevity over the whole cohort of patients awaiting transplant is negligible, because although there may be an increase in longevity in those who develop HCC, it is countered by the loss of longevity in other patients on the waiting list whose transplants are delayed so that the patient with HCC can have priority. In contrast, identification of HCC that exceeds guidelines, and resultant de-listing of such patients, is beneficial to other patients on the waiting list. Another analysis suggested that there were benefits to treating patients with HCC

on the transplant waiting list with either resection or local ablation. The benefit depended in part on the length of the waiting list. The longer the wait, the greater the benefit of intervention.

Combined use of AFP and ultrasonography increases detection rates, but also increases costs and false-positive rates. AFP-only surveillance had a 5.0% false-positive rate, ultrasound alone had a 2.9% false-positive rate, but in combination the false-positive rate was 7.5%. Ultrasound alone cost about \$2000 per tumor found, whereas the combination cost about \$3000 per tumor found.

### Priority Listing for Transplantation

Patients with small tumors can have ablation either by percutaneous ethanol injection, radiofrequency or any other technique and statistical modeling has shown that such intervention is cost-effective if the expected waiting time is longer than 6 months.

### Living Donor Orthotopic Transplantation

This is especially relevant for patients with hepatitis C virus infection in whom the potential severe recurrent liver disease is a matter of controversy. Decision analysis taking into account the risk of drop-out while waiting (4% per month), the expected survival of the recipient (70% at 5 years) and the risk for the donor (0.3%-0.5% mortality) suggest that this is a cost-effective approach if the waiting time exceeds 7 months.

## METHOD OF GUIDELINE VALIDATION

Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

The levels of evidence supporting the recommendations (Levels I, II-1, II-2, II-3, and III) are defined at the end of the "Major Recommendations" field.

#### Surveillance for Hepatocellular Carcinoma (HCC)

1. Patients at high risk for developing HCC should be entered into surveillance programs (Level I). The at-risk groups are identified in the table below.
2. Patients on the transplant waiting list should be screened for HCC because in the USA the development of HCC gives increased priority for orthotopic liver transplantation (OLT), and because failure to screen for HCC means that patients may develop HCC and progress beyond listing criteria without the physician being aware (Level III).

3. Surveillance for HCC should be performed using ultrasonography (Level II).
4. Alphafetoprotein (AFP) alone should not be used for screening unless ultrasound is not available (Level II).
5. Patients should be screened at 6 to 12 month intervals (Level II).
6. The surveillance interval does not need to be shortened for patients at higher risk of HCC (Level III).

Table. Surveillance Is Recommended for the Following Groups of Patients (Level III)

Hepatitis B carriers
<ul style="list-style-type: none"> <li>• Asian males <math>\geq 40</math> years</li> <li>• Asian females <math>\geq 50</math> years</li> <li>• All cirrhotic hepatitis B carriers</li> <li>• Family history of HCC</li> <li>• Africans over age 20</li> </ul> <p>For non-cirrhotic hepatitis B carriers not listed above the risk of HCC varies depending on the severity of the underlying liver disease, and current and past hepatic inflammatory activity. Patients with high hepatitis B virus (HBV) deoxyribonucleic acid (DNA) concentrations and those with ongoing hepatic inflammatory activity remain at risk for HCC.</p>
Non-hepatitis B cirrhosis
<ul style="list-style-type: none"> <li>• Hepatitis C</li> <li>• Alcoholic cirrhosis</li> <li>• Genetic hemochromatosis</li> <li>• Primary biliary cirrhosis</li> <li>• Although the following groups have an increased risk of HCC no recommendations for or against surveillance can be made because a lack of data precludes an assessment of whether surveillance would be beneficial. <ul style="list-style-type: none"> <li>• Alpha1-antitrypsin deficiency</li> <li>• Non-alcoholic steatohepatitis</li> <li>• Autoimmune hepatitis</li> </ul> </li> </ul>

### Diagnosis of HCC

7. Nodules found on ultrasound surveillance that are smaller than 1 cm should be followed with ultrasound at intervals from 3 to 6 months (Level III). If there has been no growth over a period of up to 2 years, one can revert to routine surveillance (Level III).
8. Nodules between 1-2 cm found on ultrasound screening of a cirrhotic liver should be investigated further with two dynamic studies, either computed tomography (CT) scan, contrast ultrasound or magnetic resonance imaging (MRI) with contrast. If the appearances are typical of HCC (i.e., hypervascular with washout in the portal/venous phase) in two techniques the lesion should be treated as HCC. If the findings are not characteristic or the vascular profile is not coincidental among techniques the lesion should be biopsied (Level II).
9. If the nodule is larger than 2 cm at initial diagnosis and has the typical features of HCC on a dynamic imaging technique, biopsy is not necessary for the diagnosis of HCC. Alternatively, if the AFP is  $>200$  ng/mL biopsy is also

not required. However, if the vascular profile on imaging is not characteristic or if the nodule is detected in a non-cirrhotic liver, biopsy should be performed (Level II).

10. Biopsies of small lesions should be evaluated by expert pathologists. If the biopsy is negative for HCC patients should be followed by ultrasound or CT scanning at 3 to 6 monthly intervals until the nodule either disappears, enlarges, or displays diagnostic characteristics of HCC. If the lesion enlarges but remains atypical for HCC a repeat biopsy is recommended (Level III).

### Staging Systems

11. To best assess the prognosis of HCC patients it is recommended that the staging system takes into account tumor stage, liver function and physical status. The impact of treatment should also be considered when estimating life expectancy. Currently, the Barcelona Clinic Liver Cancer (BCLC) system is the only staging system that accomplishes these aims (Level II-2).

### Treatment of HCC

#### Surgical Resection

12. Patients who have a single lesion can be offered surgical resection if they are non-cirrhotic or have cirrhosis but still have well preserved liver function, normal bilirubin and hepatic vein pressure gradient <10 mmHg (Level II).
13. Pre or post-resection adjuvant therapy is not recommended (Level II)

#### Liver Transplantation

14. Liver transplantation is an effective option for patients with HCC corresponding to the Milan criteria: solitary tumor  $\leq 5$  cm or up to three nodules <3 cm (Level II). Living donor transplantation can be offered for HCC if the waiting time is long enough to allow tumor progression leading to exclusion from the waiting list (Level II).
15. No recommendation can be made regarding expanding the listing criteria beyond the standard Milan Criteria (Level III).
16. Preoperative therapy can be considered if the waiting list exceeds 6 months (Level II).

#### Percutaneous Ablation

17. Local ablation is safe and effective therapy for patients who cannot undergo resection, or as a bridge to transplantation (Level II).
18. Alcohol injection and radiofrequency are equally effective for tumors <2 cm. However, the necrotic effect of radiofrequency is more predictable in all tumor sizes and in addition, its efficacy is clearly superior to that of alcohol injection in larger tumors (Level I).

#### Transarterial Embolization and Chemoembolization



19. Transarterial chemoembolization (TACE) is recommended as first line non-curative therapy for non-surgical patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread (Level I).
20. Tamoxifen, antiandrogens, octreotide or hepatic artery ligation/embolization are not recommended (Level I). Other options such as radio-labeled Yttrium glass beads, radio-labeled lipiodol or immunotherapy cannot be recommended as standard therapy for advanced HCC outside clinical trials.
21. Systemic or selective intra-arterial chemotherapy is not recommended and should not be used as standard of care (Level II).

#### Definitions:

#### Levels of Evidence According to Study Design

I: Randomized controlled trials

II-1: Controlled trials without randomization

II-2: Cohort or case-control analytic studies

II-3: Multiple time series, dramatic uncontrolled experiments

III: Opinion of respected authorities, descriptive epidemiology

#### CLINICAL ALGORITHM(S)

Algorithms are provided in the original guideline document for:

- Investigation of a nodule found on ultrasound during screening or surveillance
- A strategy for staging and treatment assignment in patients diagnosed with hepatocellular carcinoma according to the Barcelona Clinic Liver Cancer (BCLC) proposal

### EVIDENCE SUPPORTING THE RECOMMENDATIONS

#### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is specifically stated for each recommendation (see "Major Recommendations" field).

### BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

#### POTENTIAL BENEFITS

Appropriate surveillance, diagnosis, staging, treatment and monitoring of hepatocellular carcinoma (HCC)

#### POTENTIAL HARMS

- A concern about thin needle liver biopsy is the risk of bleeding and needle track seeding
- Procedure-related morbidity and mortality
- Side effects and complications from therapeutic agents

## CONTRAINDICATIONS

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Transarterial embolization (TAE) and transarterial chemoembolization (TACE) are considered for patients with nonsurgical hepatocellular carcinoma that are also ineligible for percutaneous ablation, provided there is no extrahepatic tumor spread. The main contraindication is the lack of portal blood flow (because of portal vein thrombosis, portosystemic anastomoses or hepatofugal flow). Patients with lobar or segmental portal vein thrombosis are poor candidates for TACE, as this will cause necrosis of the tumor and of the non-tumorous liver deprived of blood supply. This increases the risk of treatment-related death due to liver failure. Patients with advanced liver disease (Child-Pugh class B or C) and/or clinical symptoms of end-stage cancer should not be considered for transarterial embolization and chemoembolization as they have an increased risk of liver failure and death.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

Intended for use by physicians, these recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

### IMPLEMENTATION TOOLS

Clinical Algorithm

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Getting Better  
Living with Illness  
Staying Healthy

#### IOM DOMAIN

Effectiveness  
Timeliness

### IDENTIFYING INFORMATION AND AVAILABILITY

#### BIBLIOGRAPHIC SOURCE(S)

Bruix J, Sherman M, Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005 Nov; 42(5): 1208-36. [322 references] [PubMed](#)

#### ADAPTATION

Not applicable: The guideline was not adapted from another source.

#### DATE RELEASED

2005 Nov

#### GUIDELINE DEVELOPER(S)

American Association for the Study of Liver Diseases - Private Nonprofit Research Organization

#### SOURCE(S) OF FUNDING

American Association for the Study of Liver Diseases

#### GUIDELINE COMMITTEE

Practice Guidelines Committee

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## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Potential conflict of interest: Nothing to report.

## GUIDELINE STATUS

This is the current release of the guideline.

## GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [American Association for the Study of Liver Diseases Web site](#).

Print copies: Available from the American Association for the Study of Liver Diseases, 1729 King Street, Suite 200; Alexandria, VA 22314; Phone: 703-299-9766; Web site: [www.aasld.org](http://www.aasld.org); e-mail: [aasld@aasld.org](mailto:aasld@aasld.org).

## AVAILABILITY OF COMPANION DOCUMENTS

None available

## PATIENT RESOURCES

None available

## NGC STATUS

This summary was completed by ECRI on July 11, 2006. The information was verified by the guideline developer on July 25, 2006.

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